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EXAMINER

FALK, ANNE MARIE

ART UNIT

PAPER NUMBER

1632

DATE MAILED: 06/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.

09/693,043

Applicant(s)

BJORKLUND, ANDERS

Examiner

Anne-Marie Falk, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 08 March 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 1-4, 6, 13 and 14 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-4, 6, 13 and 14 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 20 October 2000 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

## Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

## Attachment(s)

- |   |   |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                    | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date. _____ | 6) <input type="checkbox"/> Other: _____  |

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### **DETAILED ACTION**

The amendment filed March 8, 2004 has been entered. Claim 2 has been amended. The remarks filed November 13, 2003 (hereinafter referred to as "the response") are considered herein.

Accordingly, Claims 1-4, 6, 13, and 14 are pending in the instant application.

The rejection of Claim 2 under 35 U.S.C. 112, second paragraph is withdrawn in view of the amendment to the claim, which now recites that "said neural stem cells are mammalian embryonic neural stem cells."

### ***Priority***

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

Applicant claims priority to provisional application 60/160,553, nonprovisional applications 09/339,093, 08/926,313, 09/486,302, and PCT/US98/18597. However, the instant application does not share an inventor in common with any of the aforementioned applications. Anders Bjorklund is the sole inventor named in the instant application and is not a named inventor in any of the aforementioned applications.

Thus, the priority claim does not meet the formal requirements of 35 U.S.C. 120 and priority is not granted. The effective filing date of the instant application is October 20, 2000.

### ***Specification***

The disclosure is objected to because it contains an improper priority claim. See above.

Appropriate correction is required.

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*Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6, 13, and 14 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record advanced on pages 2-9 of the Office Action mailed 5/12/03 and on pages 2-5 of the Office Action mailed 7/16/02, and for further reasons as discussed herein, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

At page 5 of the response, Applicant asserts that one of ordinary skill in the art would be able to routinely use the described methods to transplant CNS stem cells and to induce migration, integration, and differentiation of these cells via infusion of a growth factor. Referring to MPEP §2164.01(c), Applicant argues that the “Examiner’s determination that the claims are not enabled fails to follow the procedures set forth in the M.P.E.P.” Applicants reproduce the following paragraph from MPEP §2164.01(c):

In contrast, **when a compound or composition claim is not limited by a recited use**, any enabled use that would reasonably correlate with the entire scope of that claim is sufficient to preclude a rejection for nonenablement based on how to use. If multiple uses for claimed compounds or compositions are disclosed in the application, than an enablement rejection must include an explanation, sufficiently supported by the evidence, why the specification fails to enable each disclosed use. In other words, if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention (emphasis added).

In the instant case, the claims are directed to methods, **not compositions**. Even from the section reproduced at page 5 of the response, it is clear that the MPEP is discussing the treatment of **composition claims not limited by a recited use**. It is well established in our law that all claims must be enabled over their full scope.

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At page 5, paragraph 3 of the response, Applicant jumps to the conclusion that the Examiner is requiring evidence that the claimed methods can be used to cure the disorders named in the application. However, the word “cure” was not mentioned in the rejection. While a cure would be considered a “therapeutic effect,” a “therapeutic effect” is clearly not the equivalent of a cure.

At page 6, paragraph 2 of the response, Applicant emphasizes that the specification expressly describes that the number of cells to be transplanted is 250,000 – 500,000 cells per deposit and that various sites of injection are contemplated, namely the striatum, parenchymal sites, and intrathecal sites. Applicant further emphasizes that the specification teaches that an infusion cannula may be placed in a lateral ventricle and that EGF may be infused. Applicants point particularly to Examples 8 and 9. In response, it is noted that Example 8 discloses that human neural stem cells were transplanted into rat brain in the left striatum and that 250,000-500,000 cells total were implanted. The specification is silent as to whether the neural stem cells used in Example 8 were from adults or embryos. Example 9 discloses that 300,000 neural stem cells were transplanted into the adult rat striatum and EGF was infused into a lateral ventricle. The specification further indicates that grafts survived for 7 days in rats receiving EGF. The example is silent with regard to the species from which the neural stem cells were isolated and is also silent as to whether the neural stem cells were from adults or embryos. The example is also silent with regard to migration of the implanted neural stem cells.

At page 6, paragraph 4 of the response, Applicant asserts that the “instant claims recite methods for transplanting neural stem cells to a first locus of the brain, wherein, following infusion of a mitogenic growth factor, the cells migrate to a second locus, integrate into the parenchymal tissue and differentiate.” Contrary to Applicant’s assertion, only Claim 4 involves migration to the second locus. The remaining claims recite migration “to other anatomic sites” which clearly includes migration away from the second locus.

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At page 6, paragraph 5 of the response, Applicant asserts that the “working examples” demonstrate the responsiveness of the transplanted cells to an EGF infusion. Applicant points specifically to Examples 9, 11, and 15. First, it is noted that Example 11 is a prophetic example and therefore cannot be said to “demonstrate” anything in terms of the response of transplanted cells. Second, it is noted that neither Example 9 nor 15 constitute a working example of the claimed invention because neither example discloses **integration** of the implanted cells nor differentiation **after integration** as the claims require. None of the experiments were directed to looking at integration, such as cell-cell contact or cell-cell communication.

At page 7, paragraph 3 of the response, Applicant asserts that the “working examples” correlate with the steps recited in the claimed methods. Applicant concludes that this is all that is required to meet the “how to use” portion of the enablement requirement. However, as discussed above, Applicant’s response makes no mention of integration of the implanted cells, which is indisputably a requirement of the claims. Furthermore, the specification does not include any examples that evaluate or even detect integration of the implanted cells. Moreover, as the only real world utility mentioned in the specification is to use the claimed method to produce a therapeutic effect, the specification must provide an enabling disclosure teaching one of skill in the art how to use the claimed invention to produce a therapeutic effect. Disclosing migration of donor cells within a host brain is not sufficient to allow one of skill in the art to make the very large leap to using the claimed method to produce a therapeutic effect.

At page 8, paragraph 1 of the response, Applicant cites *In re Marzocchi*, asserting that “it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up any assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.” In the instant case, ample reasons have been given to doubt that one skilled in the art could, using only routine experimentation as opposed to undue experimentation, use the claimed invention to produce a therapeutic

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effect. As detailed in the previous Office Actions, intensive investigation has been applied by many researchers, using a variety of protocols, in an effort to transplant neural stem cells, as well as other neural progenitor cells, to achieve a therapeutic effect. While the PTO bears the initial burden of providing reasons for doubting the objective truth of the statements made by Applicants as to the scope of enablement, when the PTO meets this burden, the burden shifts to applicant to provide suitable evidence indicating that the specification is enabling in a manner commensurate in scope with the protection sought by the claims. *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971).

At page 8, paragraph 2 of the response, Applicant refers to Milward (1997), Zhang (1999), Brustle (1998), and Yandava (1999), and states that, in those papers, a therapeutic effect “was simply not measured or reported – but that does not mean it was not achieved.” However, this is not true, as Milward (1997) clearly discloses that the clinical deficit was not ameliorated and the experiments of Brustle (1998) were carried out in healthy animals, and therefore *could not* produce a therapeutic effect. Furthermore, as discussed in the previous Office Action Yandava (1999) discloses transplantation of a **cloned cell line** from neonatal mouse **cerebellum** (p. 7030, column 1, paragraph 3), and therefore cannot support enablement for the claimed method.

At page 8, paragraph 3 of the response, Applicant reiterates their argument with regard to the reference of Akiyama (2001). This argument has already been answered in detail at pages 5-6 of the Office Action mailed 5/12/03.

At page 9, paragraphs 1-3 of the response, Applicant cites Pluchino et al. (2003, Nature 422: 688-694) for providing conclusive evidence of a therapeutic benefit. However, Pluchino does not disclose the claimed invention, which requires administration of “a mitogenic growth factor that does not induce differentiation.” Rather, Pluchino teaches intravenous and intracerebroventricular administration of  $1 \times 10^6$  neural precursors in the context of an EAE model. The instant specification broadly contemplates administering neural stem cells to sites in the parenchyma and intrastriatal injection, but does not

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contemplate intravenous or intracerebroventricular administration. Furthermore, the examples describe the administration of 300,000 to 500,000 cells, and while the claims broadly recite transplanting at least about 500,000 cells, the specification does not direct one of skill in the art to implant  $1 \times 10^6$  neural precursors by the routes of administration taught by Pluchino. The experiments of Pluchino do not involve the administration of a mitogenic growth factor, as required by the instant claims. Thus, the protocol of Pluchino is substantially different from what is taught in the instant specification and, given that Pluchino is post-filing art, the skilled artisan would not have had the benefit of the teachings of Pluchino at the time the instant application was filed.

At page 9, paragraph 4 of the response, Applicant dismisses Jackowski et al. (1995) as “nonanalogous art.” The Examiner does not agree with this characterization. Jackowski details the limitations and unpredictability associated with the transplantation of neural tissue, particularly within the CNS. This is clearly the relevant art of inquiry. At page 311, column 1, paragraph 2, the reference discusses barriers to successful transplantation of neural tissue, notably the presence of molecules that directly inhibit the regeneration of mammalian CNS axons. Thus, the teachings are of clear importance in the art of neural cell transplantation. The instant specification does not provide guidance for overcoming the problems recognized in the art.

Given the lack of applicable working examples, the limited guidance provided in the specification, the broad scope of the claims with regard to the regions of the brain to be treated, and the unpredictability for achieving a therapeutic effect upon the transplantation of neural stem cells, undue experimentation would have been required for one skilled in the art to practice the claimed method of the invention to achieve a therapeutic effect, the only real world utility asserted in the specification.

Thus, the rejection under 35 U.S.C. 112, first paragraph, is maintained.



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*Conclusion*

No claims are allowed.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 10:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached on (571) 272-0804. The central official fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Dianiece Jacobs, whose telephone number is (571) 272-0532.

Anne-Marie Falk, Ph.D.



**ANNE-MARIE FALK, PH.D**  
**PRIMARY EXAMINER**